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I, TERESA KOLODZIEJCZYK, TEAM LEADER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. PP 7706 for a patent by FUJISAWA PHARMACEUTICAL CO., LTD. as filed on 14 December 1998.

WITNESS my hand this
Sixth day of January 2003

A handwritten signature in black ink, appearing to be "e. c." followed by a long horizontal flourish.

TERESA KOLODZIEJCZYK
TEAM LEADER EXAMINATION
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Fujisawa Pharmaceutical Co., Ltd.

A U S T R A L I A
Patents Act 1990

PROVISIONAL SPECIFICATION
for the invention entitled:

"Piperazine Derivatives"

The invention is described in the following statement:

DESCRIPTION

PIPERAZINE DERIVATIVES

5 TECHNICAL FIELD

The present invention relates to new piperazine derivatives and a salt thereof.

More particularly, it relates to new piperazine derivatives and a salt thereof which have pharmacological
10 activities such as Tachykinin antagonism, especially Substance P antagonism, Neurokinin A antagonism, Neurokinin B antagonism, and the like, to a process for preparation thereof, to a pharmaceutical composition comprising the same, and to a use of the same as a medicament.

15 Accordingly, one object of the present invention is to provide new and useful piperazine derivatives and a salt thereof which have pharmacological activities such as Tachykinin antagonism, especially Substance P antagonism, Neurokinin A antagonism, Neurokinin B antagonism, and the
20 like.

Another object of the present invention is to provide a process for the preparation of said piperazine derivatives and a salt thereof.

A further object of the present invention is to provide
25 a pharmaceutical composition comprising, as an active ingredient, said piperazine derivatives and a pharmaceutically acceptable salt thereof.

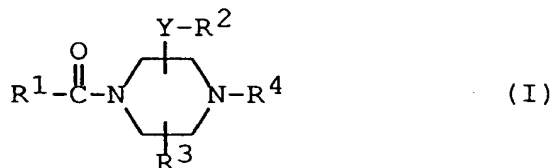
Still further object of the present invention is to provide a use of said piperazine derivatives or a
30 pharmaceutically acceptable salt thereof as Tachykinin antagonist, especially Substance P antagonist, Neurokinin A antagonist or Neurokinin B antagonist, useful for treating or preventing Tachykinin-mediated diseases, for example, respiratory diseases such as asthma, bronchitis, rhinitis,
35 cough, expectoration, and the like; ophthalmic diseases such

as conjunctivitis, vernal conjunctivitis, and the like;
 cutaneous diseases such as contact dermatitis, atopic
 dermatitis, urticaria, and other eczematoid dermatitis, and
 the like; inflammatory diseases such as rheumatoid arthritis,
 5 osteoarthritis, and the like; pains or aches (e.g., migraine,
 headache, toothache, cancerous pain, back pain, etc.); and
 the like in human being or animals.

Some piperazine derivatives having pharmaceutical
 10 activities such as Tachykinin antagonism have been known as
 described in EP 0655442 A1 and WO 97/22597 A1.

DISCLOSURE OF INVENTION

The object compound of the present invention can be
 15 represented by the following general formula (I) :



20 wherein

Y is bond or lower alkylene,

R¹ is aryl which may be substituted with suitable
 substituent(s),

25 R² is aryl or indolyl, each of which may be substituted with
 suitable substituent(s),

R³ is hydrogen or lower alkyl,

R⁴ is (3-pyridyl)methyl;

(3-pyridyl)ethyl;

30 3-(3-pyridyl)propyl;

3-(3-pyridyl)propenyl;

3-(3-pyridyl)propynyl;

pyrazolylmethyl which may be substituted with

hydroxy(lower)alkyl;

35 pyrazolyl(lower)alkyl which is substituted with lower

alkyl, (lower)alkoxy(lower)alkylmorpholinyl(lower)alkyl
or (lower)alkoxy(lower)alkylmorpholinylcarbonyl(lower)-
alkyl;

piperidylmethyl;

5 piperidyl(lower)alkyl which is substituted with lower
alkyl or (lower)alkoxy(lower)alkyl;

(2,6-dimethylmorpholino)(lower)alkyl;

(3,3-dimethylmorpholino)(lower)alkyl;

(cis-3,5-dimethylmorpholino)(lower)alkyl;

10 ((3S,5S)-3,5-dimethylmorpholino)(lower)alkyl;

(2-methoxymethylmorpholino)(lower)alkyl;

(3-methoxymethylmorpholino)(lower)alkyl;

(2-methoxymethyl-5-methylmorpholino)(lower)alkyl;

(2-methoxymethyl-5,5-dimethylmorpholino)(lower)alkyl;

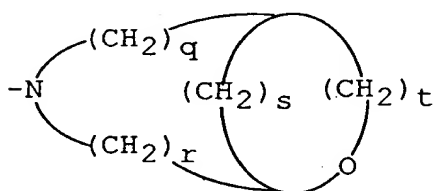
15 (3,5-dimethoxymethylmorpholino)(lower)alkyl;

(2,3-dimethoxymethylmorpholino)(lower)alkyl;

(2-methoxymethylmorpholino)(lower)alkenyl;

(5,6,7,8-tetrahydro-1,6-naphthyridin-6-yl)(lower)alkyl;

20 or lower alkyl which is substituted with a saturated
heterocyclic group of the formula :



(wherein

r, s and t are each integer
of 1 to 2, and

q is integer of 0 to 2)

25 which may be substituted with one or two lower alkyl.

30 It is to be noted that the object compound (I) may
include one or more stereoisomers due to asymmetric carbon
atom(s) and double bond, and all of such isomers and a
mixture thereof are included within the scope of the present
invention.

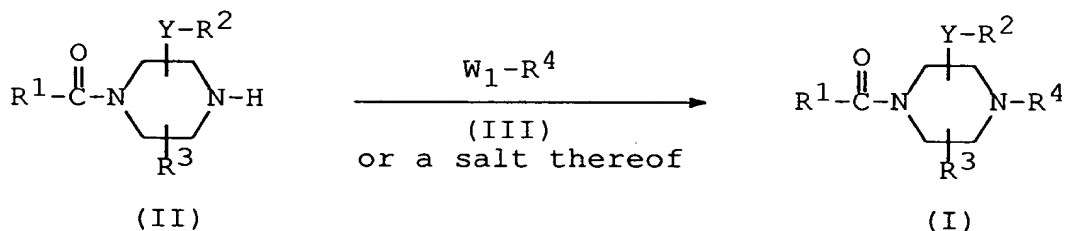
35 It is further to be noted that isomerization or
rearrangement of the object compound (I) may occur due to the

effect of the light, acid, base or the like, and the compound obtained as the result of said isomerization or rearrangement is also included within the scope of the present invention.

It is also to be noted that the solvating form of the compound (I) (e.g. hydrate, etc.) and any form of the crystal of the compound (I) are included within the scope of the present invention.

According to the present invention, the object compound (I) or a salt thereof can be prepared by processes which are illustrated in the following schemes.

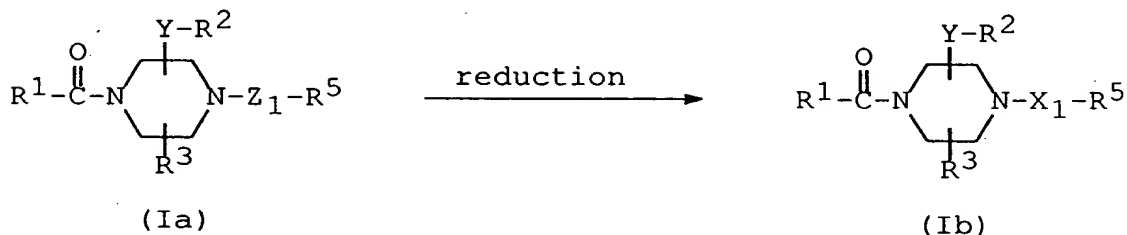
Process 1



or its reactive derivative
at the imino group
or a salt thereof

or a salt thereof

Process 2



or a salt thereof

or a salt thereof

wherein

Y, R¹, R², R³ and R⁴ are each as defined above,

X₁ is lower alkylene,

Z₁ is lower alkynylene,

R⁵ is 3-pyridyl, and

W_1 is a leaving group.

As to the starting compounds (II) and (III), some of them are novel and can be prepared by the procedures described in the Preparations and Examples mentioned later or similar manners thereto.

Suitable salts of the starting and object compounds are conventional non-toxic and pharmaceutically acceptable salt and include an acid addition salt such as an organic acid salt (e.g. acetate, trifluoroacetate, fumarate, maleate, tartrate, methanesulfonate, benzenesulfonate, formate, toluenesulfonate, etc.), an inorganic acid salt (e.g. hydrochloride, hydrobromide, hydroiodide, sulfate, nitrate, phosphate, etc.), or a salt with an amino acid (e.g. arginine, aspartic acid, glutamic acid, etc.), or a metal salt such as an alkali metal salt (e.g. sodium salt, potassium salt, etc.) and an alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc.), an ammonium salt, an organic base salt (e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.), or the like.

In the above and subsequent descriptions of the present specification, suitable examples and illustrations of the various definitions which the present invention intends to include within the scope thereof are explained in detail as follows.

The term "lower" is intended to mean 1 to 6, preferably 1 to 4, carbon atom(s), unless otherwise indicated.

Suitable "lower alkylene" may include straight or branched one having 1 to 6 carbon atom(s), such as methylene, ethylene, trimethylene, propylene, tetramethylene, methylnmethylene, methyltrimethylene, hexamethylene, and the

like, in which the preferred one is methylene, ethylene, trimethylene or methylenemethylene.

Suitable "lower alkynylene" may include one having 2 to 6 carbon atoms, such as ethynylene, propynylene, butynylene, and the like, in which the preferred one is propynylene or butynylene.

Suitable "halogen" and "halogen" moiety in the terms "mono(or di or tri)halo(lower)alkyl", "mono(or di or tri)halo(C₁-C₄)alkyl", etc. may include fluorine, chlorine, bromine and iodine.

Suitable "lower alkyl" and "lower alkyl" moiety in the terms "hydroxy(lower)alkyl", "pyrazolyl(lower)alkyl", etc. may include straight or branched one having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl and the like, in which the preferred one is C₁-C₄ alkyl and the most preferred one is methyl or isopropyl.

Suitable "lower alkenyl" moiety in the term "(2-methoxymethylmorpholino)(lower)alkenyl" may include vinyl, 1-(or 2-)propenyl, 1-(or 2- or 3-)butenyl, 1-(or 2- or 3- or 4-)pentenyl, 1-(or 2- or 3- or 4- or 5-)hexenyl, methylvinyl ethylvinyl, 1-(or 2- or 3-)methyl-1-(or 2-)propenyl, 1-(or 2- or 3-)ethyl-1-(or 2-)propenyl, 1-(or 2- or 3- or 4-)methyl-1-(or 2- or 3-)butenyl, and the like, in which more preferable example may be C₂-C₄ alkenyl.

Suitable "aryl" may include phenyl, naphthyl, and the like, in which the preferred one is C₆-C₁₀ aryl and the most preferred one is phenyl or naphthyl.

Suitable "lower alkoxy" and "lower alkoxy" moiety in the terms "(lower)alkoxy(lower)alkylmorpholinyl(lower)alkyl", "(lower)alkoxy(lower)alkylmorpholinylcarbonyl(lower)alkyl", etc. may include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, t-butoxy, pentyloxy, t-pentyloxy, hexyloxy and the like, in which the preferred one is C₁-C₄ alkoxy and

the most preferred one is methoxy.

Suitable "substituent" in the terms "aryl which may be substituted with suitable substituent(s)" for R^1 and "aryl or indolyl, each of which may be substituted with suitable substituent(s)" for R^2 may include lower alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, neopentyl, tert-pentyl, hexyl, etc.), lower alkylenedioxy (e.g., methylenedioxy, ethylenedioxy, propylenedioxy, etc.), lower alkoxy (e.g., methoxy, ethoxy, propoxy, isopropoxy, isobutoxy, tert-butoxy, pentyloxy, neopentyloxy, tert-pentyloxy, hexyloxy, etc.), lower alkoxy(lower)alkoxy(lower)alkoxy (e.g., (2-methoxyethoxy)-methoxy, etc.), mono(or di or tri)halo(lower)alkyl (e.g., fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, bromomethyl, dibromomethyl, tribromomethyl, 1 or 2-fluoroethyl, 1 or 2-bromoethyl, 1 or 2-chloroethyl, 1,1-difluoroethyl, 2,2-difluoroethyl, etc.), halogen (e.g., chlorine, bromine, fluorine and iodine), hydroxy, hydroxy(lower)alkyl (e.g., hydroxymethyl, hydroxyethyl, 1-hydroxy-1-methylethyl, etc.), cyano, lower alkylthio (e.g., methylthio, ethylthio, propylthio, isopropylthio, butylthio, etc.), lower alkylsulfonyl (e.g., methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, etc.), di(lower alkyl)aminosulfonyl (e.g., dimethylaminosulfonyl, diethylaminosulfonyl, etc.), pyrrolidinyl (e.g., 2-pyrrolidinyl, 3-pyrrolidinyl, pyrrolidino, etc.), morpholinyl (e.g., 2-morpholinyl, 3-morpholinyl, morpholino which may be substituted with lower alkyl as mentioned above or lower alkoxy(lower)alkyl (e.g., methoxymethyl, ethoxymethyl, 1-methoxyethyl, 2-methoxyethyl, 1-ethoxyethyl, 2-ethoxyethyl, etc.), pyrrolyl (e.g., 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, etc.), pyridyl (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl, etc.), and the like.

Suitable "leaving group" may include lower alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, t-butoxy, pentoxy, etc.), aryloxy (e.g., phenoxy, naphthoxy, etc.), an acid residue or the like.

5 Suitable "acid residue" may be halogen (e.g., chlorine, bromine, iodine, etc.), sulfonyloxy (e.g., methanesulfonyloxy, phenylsulfonyloxy, mesitylenesulfonyloxy, toluenesulfonyloxy, etc.) or the like.

10 Preferred embodiments of the object compound (I) are as follows :

Y is lower alkylene (more preferably C₁-C₄ alkylene, most preferably methylene);

15 R¹ is aryl (more preferably C₆-C₁₀ aryl, most preferably phenyl) which may be substituted with 1 to 3 (more preferably 1 or 2, most preferably 2) substituent(s) [more preferably substituent selected from the group consisting of lower alkoxy (more preferably C₁-C₄ alkoxy, most preferably methoxy), mono(or di or tri)-

20 halo(lower)alkyl (more preferably trihalo(lower)alkyl, most preferably trifluoromethyl); lower alkylthio (more preferably C₁-C₄ alkylthio, most preferably methylthio), lower alkylsulfonyl (more preferably C₁-C₄ alkylsulfonyl, most preferably methylsulfonyl), di(lower

25 alkyl)aminosulfonyl (more preferably di(C₁-C₄ alkyl)aminosulfonyl, most preferably dimethylaminosulfonyl), pyrrolyl (more preferably 1-pyrrolyl) and pyridyl (more preferably 4-pyridyl)];

30 R² is aryl (more preferably C₆-C₁₀ aryl, most preferably phenyl or naphthyl) or indolyl, each of which may be substituted with 1 to 3 (more preferably 1 or 2) substituent(s) [more preferably substituent selected from the group consisting of lower alkyl (more

35 preferably C₁-C₄ alkyl, most preferably methyl or

isopropyl), mono(or di or tri)halo(lower)alkyl (more preferably mono(or di or tri)halo(C₁-C₄)alkyl, most preferably difluoromethyl or trifluoromethyl), halogen (more preferably chlorine or fluoride), lower
 5 alkylenedioxy (more preferably C₁-C₄ alkylenedioxy, most preferably methylenedioxy or ethylenedioxy), lower alkoxy(lower)alkoxy(lower)alkoxy (more preferably C₁-C₄ alkoxy(C₁-C₄)alkoxy(C₁-C₄)alkoxy, most preferably (2-methoxyethoxy)methoxy), hydroxy, hydroxy(lower)alkyl
 10 (more preferably hydroxy(C₁-C₄)alkyl, most preferably hydroxymethyl or 1-hydroxy-1-methylethyl), cyano, pyrrolidinyl (more preferably pyrrolidino) and morpholinyl (more preferably morpholino) which may be substituted with lower alkoxy(lower)alkyl (more
 15 preferably C₁-C₄ alkoxy(C₁-C₄)alkyl, most preferably methoxymethyl) or lower alkyl (more preferably C₁-C₄ alkyl, most preferably methyl)];

R³ is hydrogen; and

R⁴ is (3-pyridyl)methyl;

20 (3-pyridyl)ethyl (more preferably 2-(3-pyridyl)ethyl);
 3-(3-pyridyl)propyl;
 3-(3-pyridyl)propenyl (more preferably 3-(3-pyridyl)-2-propenyl);
 3-(3-pyridyl)propynyl (more preferably 3-(3-pyridyl)-2-propynyl);
 25 pyrazolylmethyl (more preferably (4-pyrazolyl)methyl or (5-pyrazolyl)methyl) which may be substituted with hydroxy(lower)alkyl (more preferably hydroxy(C₁-C₄)-alkyl, most preferably 2-hydroxyethyl);
 30 pyrazolyl(lower)alkyl (more preferably pyrazolyl-(C₁-C₄)alkyl, most preferably (4-pyrazolyl)methyl, (5-pyrazolyl)methyl or 3-(4-pyrazolyl)propyl) which is substituted with lower alkyl (more preferably C₁-C₄ alkyl, most preferably methyl), (lower)alkoxy(lower)-
 35 alkylmorpholinyl(lower)alkyl (more preferably (C₁-C₄)-

alkoxy(C₁-C₄)alkylmorpholinyl(C₁-C₄)alkyl, most preferably 2-(2-methoxymethylmorpholino)ethyl) or (lower)alkoxy(lower)alkylmorpholinylcarbonyl(lower)alkyl (more preferably (C₁-C₄)alkoxy(C₁-C₄)-

5 alkylmorpholinylcarbonyl(C₁-C₄)alkyl, most preferably (2-methoxymethylmorpholino)carbonylmethyl); piperidylmethyl (more preferably (4-piperidyl)methyl); piperidyl(lower)alkyl (more preferably piperidyl(C₁-C₄)-alkyl, most preferably piperidinomethyl or

10 (4-piperidyl)methyl) which is substituted with lower alkyl (more preferably C₁-C₄ alkyl, most preferably methyl) or (lower)alkoxy(lower)alkyl (more preferably (C₁-C₄)alkoxy(C₁-C₄)alkyl, most preferably ethoxymethyl);

15 (2,6-dimethylmorpholino)(lower)alkyl (more preferably (2,6-dimethylmorpholino)(C₁-C₄)alkyl, most preferably 2-(2,6-dimethylmorpholino)ethyl); (3,3-dimethylmorpholino)(lower)alkyl (more preferably (3,3-dimethylmorpholino)(C₁-C₄)alkyl, most preferably

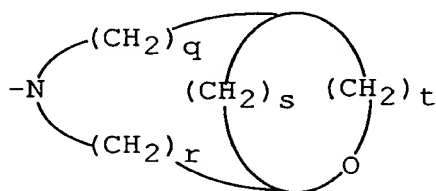
20 2-(3,3-dimethylmorpholino)ethyl); (cis-3,5-dimethylmorpholino)(lower)alkyl (more preferably (cis-3,5-dimethylmorpholino)(C₁-C₄)alkyl, most preferably 2-(cis-3,5-dimethylmorpholino)ethyl); ((3S,5S)-3,5-dimethylmorpholino)(lower)alkyl (more

25 preferably ((3S,5S)-3,5-dimethylmorpholino)(C₁-C₄)alkyl, most preferably 2-((3S,5S)-3,5-dimethylmorpholino)-ethyl); (2-methoxymethylmorpholino)(lower)alkyl (more preferably (2-methoxymethylmorpholino)(C₁-C₄)alkyl, most preferably

30 3-(2-methoxymethylmorpholino)propyl or 2-(2-methoxymethylmorpholino)ethyl); (3-methoxymethylmorpholino)(lower)alkyl (more preferably (3-methoxymethylmorpholino)(C₁-C₄)alkyl, most preferably 2-(3-methoxymethylmorpholino)ethyl);

35 (2-methoxymethyl-5-methylmorpholino)(lower)alkyl (more

preferably (2-methoxymethyl-5-methylmorpholino)-
 (C₁-C₄)alkyl, most preferably 2-(2-methoxymethyl-5-
 methylmorpholino)ethyl);
 (2-methoxymethyl-5,5-dimethylmorpholino)(lower)alkyl
 (more preferably (2-methoxymethyl-5,5-
 dimethylmorpholino)(C₁-C₄)alkyl, most preferably 2-(2-
 methoxymethyl-5,5-dimethylmorpholino)ethyl);
 (3,5-dimethoxymethylmorpholino)(lower)alkyl (more
 preferably (3,5-dimethoxymethylmorpholino)(C₁-C₄)alkyl,
 most preferably 2-(3,5-dimethoxymethylmorpholino)ethyl);
 (2,3-dimethoxymethylmorpholino)(lower)alkyl (more
 preferably (2,3-dimethoxymethylmorpholino)(C₁-C₄)alkyl,
 most preferably 2-(2,3-dimethoxymethylmorpholino)ethyl);
 (2-methoxymethylmorpholino)(lower)alkenyl (more
 preferably (2-methoxymethylmorpholino)(C₂-C₄)alkenyl,
 most preferably 4-(2-methoxymethylmorpholino)-2-
 butenyl);
 (5,6,7,8-tetrahydro-1,6-naphthyridin-6-yl)(lower)alkyl
 (more preferably (5,6,7,8-tetrahydro-1,6-naphthyridin-6-
 yl)(C₁-C₄)alkyl, most preferably 2-(5,6,7,8-tetrahydro-
 1,6-naphthyridin-6-yl)ethyl); or
 lower alkyl (more preferably C₁-C₄ alkyl, most
 preferably ethyl) which is substituted with a saturated
 heterocyclic group of the formula :



(wherein

r, s and t are each integer
 of 1 to 2, and

q is integer of 0 to 2)

(more preferably (1S,4S)-2-aza-5-oxabicyclo[2.2.1]-
 heptan-2-yl) which may be substituted with one or two
 lower alkyl (more preferably C₁-C₄ alkyl, most
 preferably methyl).

More preferred embodiments of the object compound (I) are as follows :

Y is lower alkylene (more preferably C₁-C₄ alkylene, most preferably methylene);

R¹ is phenyl which may be substituted with 1 or 2 substituent(s) selected from the group consisting of lower alkoxy, mono(or di or tri)halo(lower)alkyl, lower alkylthio, lower alkylsulfonyl, di(lower alkyl)-aminosulfonyl, pyrrolyl and pyridyl [more preferably bis(trihalo(lower)alkyl)phenyl, (trihalo(lower)alkyl)((lower)alkoxy)phenyl, (trihalo(lower)alkyl)((lower)alkylthio)phenyl, (trihalo(lower)alkyl)((lower)alkylsulfonyl)phenyl, (trihalo(lower)alkyl)(di(lower alkyl)aminosulfonyl)-phenyl, (trihalo(lower)alkyl)(pyrrolyl)phenyl or (trihalo(lower)alkyl)(pyridyl)phenyl, most preferably 3,5-bis(trifluoromethyl)phenyl, 3-methoxy-5-trifluoromethylphenyl, 3-methylthio-5-trifluoromethylphenyl, 3-methylsulfonyl-5-trifluoromethylphenyl, 3-dimethylaminosulfonyl-5-trifluoromethylphenyl, 3-(1-pyrrolyl)-5-trifluoromethylphenyl or 3-(4-pyridyl)-5-trifluoromethylphenyl];

R² is phenyl which may be substituted with 1 or 2 substituent(s) selected from the group consisting of lower alkyl, mono(or di or tri)halo(lower)alkyl, halogen, lower alkylenedioxy, lower alkoxy(lower)alkoxy(lower)alkoxy, hydroxy, hydroxy(lower)alkyl, cyano, pyrrolidinyl and morpholinyl which may be substituted with lower alkoxy(lower)alkyl or lower alkyl [more preferably (lower)alkylenedioxy)phenyl, halophenyl, [trihalo(lower)alkyl]phenyl, (halo)((lower)alkyl)phenyl, (halo)(hydroxy)phenyl, [trihalo(lower)alkyl](hydroxy)-

phenyl, [hydroxy(lower)alkyl](hydroxy)phenyl,
 (cyano)(hydroxy)phenyl, (dihalo(lower)alkyl)(hydroxy)-
 phenyl, (lower alkyl)(hydroxy)phenyl, (lower
 alkyl)(pyrrolidinyl)phenyl, (lower
 5 alkyl)(morpholinyl)phenyl, (lower alkyl)[(lower)alkoxy-
 (lower)alkylmorpholinyl]phenyl or (lower alkyl)[(lower
 alkyl)morpholinyl]phenyl, most preferably 1,4-
 benzodioxan-6-yl, 4-fluorophenyl, 4-trifluorophenyl,
 4-fluoro-3-methylphenyl, 3-fluoro-4-methylphenyl,
 10 4-chloro-3-hydroxyphenyl, 3-hydroxy-4-
 trifluoromethylphenyl, 3-hydroxy-4-hydroxymethylphenyl,
 3-hydroxy-4-(1-hydroxy-1-methylethyl)phenyl,
 4-cyano-3-hydroxyphenyl, 3-hydroxy-4-difluoromethyl-
 phenyl, 3-hydroxy-4-isopropylphenyl, 4-methyl-3-
 15 pyrrolidinophenyl or 4-methyl-3-morpholinophenyl] or
 indolyl;

R³ is hydrogen; and

R⁴ is (2,6-dimethylmorpholino)(lower)alkyl (more preferably
 (2,6-dimethylmorpholino)(C₁-C₄)alkyl, most preferably
 20 2-(2,6-dimethylmorpholino)ethyl);
 (3,3-dimethylmorpholino)(lower)alkyl (more preferably
 (3,3-dimethylmorpholino)(C₁-C₄)alkyl, most preferably
 2-(3,3-dimethylmorpholino)ethyl);
 (cis-3,5-dimethylmorpholino)(lower)alkyl (more
 25 preferably (cis-3,5-dimethylmorpholino)(C₁-C₄)alkyl,
 most preferably 2-(cis-3,5-dimethylmorpholino)ethyl);
 ((3S,5S)-3,5-dimethylmorpholino)(lower)alkyl (more
 preferably ((3S,5S)-3,5-dimethylmorpholino)(C₁-C₄)alkyl,
 most preferably 2-((3S,5S)-3,5-dimethylmorpholino)-
 30 ethyl);
 (2-methoxymethylmorpholino)(lower)alkyl (more preferably
 (2-methoxymethylmorpholino)(C₁-C₄)alkyl, most preferably
 3-(2-methoxymethylmorpholino)propyl or
 2-(2-methoxymethylmorpholino)ethyl);
 35 (3-methoxymethylmorpholino)(lower)alkyl (more preferably

(3-methoxymethylmorpholino) (C₁-C₄) alkyl, most preferably 2-(3-methoxymethylmorpholino) ethyl);

(2-methoxymethyl-5-methylmorpholino) (lower) alkyl (more preferably (2-methoxymethyl-5-methylmorpholino) (C₁-C₄) alkyl, most preferably 2-(2-methoxymethyl-5-methylmorpholino) ethyl);

(2-methoxymethyl-5,5-dimethylmorpholino) (lower) alkyl (more preferably (2-methoxymethyl-5,5-dimethylmorpholino) (C₁-C₄) alkyl, most preferably 2-(2-methoxymethyl-5,5-dimethylmorpholino) ethyl);

(3,5-dimethoxymethylmorpholino) (lower) alkyl (more preferably (3,5-dimethoxymethylmorpholino) (C₁-C₄) alkyl, most preferably 2-(3,5-dimethoxymethylmorpholino) ethyl);

(2,3-dimethoxymethylmorpholino) (lower) alkyl (more preferably (2,3-dimethoxymethylmorpholino) (C₁-C₄) alkyl, most preferably 2-(2,3-dimethoxymethylmorpholino) ethyl);

or (2-methoxymethylmorpholino) (lower) alkenyl (more preferably (2-methoxymethylmorpholino) (C₂-C₄) alkenyl, most preferably 4-(2-methoxymethylmorpholino)-2-butenyl).

The Processes 1 and 2 for preparing the object compound (I) of the present invention are explained in detail in the following.

Process 1

The object compound (I) or a salt thereof can be prepared by reacting the compound (II) or its reactive derivative at the imino group or a salt thereof with the compound (III) or a salt thereof.

Suitable reactive derivative at the imino group of the compound (II) may include Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the compound (II) with a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction

of the compound (II) with a silyl compound such as bis(trimethylsilyl)acetamide, mono(trimethylsilyl)acetamide, bis(trimethylsilyl)urea or the like; a derivative formed by reaction of the compound (II) with phosphorus trichloride or phosgene and the like.

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g. methanol, ethanol, etc.], acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction. These conventional solvents may also be used in a mixture with water.

The reaction may also be carried out in the presence of an inorganic or organic base such as alkali metal carbonate, alkali metal bicarbonate, tri(lower)alkylamine, pyridine, N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, or the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to heating.

Process 2

The object compound (Ib) or a salt thereof can be prepared by subjecting the compound (Ia) or a salt thereof to a reduction reaction.

The reaction can be carried out in the manner disclosed in Example 8 mentioned later or similar manners thereto.

The object compound (I) and a pharmaceutically acceptable salt thereof have pharmacological activities such as Tachykinin antagonism, especially Substance P antagonism, Neurokinin A antagonism or Neurokinin B antagonism, and therefore are useful for treating or preventing Tachykinin-mediated diseases, particularly Substance P-mediated diseases, for example, respiratory diseases such as asthma,

bronchitis (e.g. chronic bronchitis, acute bronchitis and diffuse panbronchiolitis, etc.), rhinitis, cough, expectoratation, and the like;

ophthalmic diseases such as conjunctivitis, vernal

5 conjunctivitis, and the like;

cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis, and the like; inflammatory diseases such as rheumatoid arthritis, osteoarthritis, and the like;

10 pains or aches (e.g. migraine, headache, cluster headache, toothache, cancerous pain, back pain, neuralgia, etc.); and the like.

Further, it is expected that the object compound (I) and a pharmaceutically acceptable salt thereof of the present invention are useful for treating or preventing ophthalmic

15 diseases such as glaucoma, uveitis, and the like; gastrointestinal diseases such as ulcer, ulcerative colitis, irritable bowel syndrome, food allergy, and the like; inflammatory diseases such as nephritis, and the like;

20 circulatory diseases such as hypertension, angina pectoris, cardiac failure, thrombosis, Raynaud's disease, and the like; epilepsy; spastic paralysis; pollakiuria; cystitis; bladder detrusor hyperreflexia; urinary incontinence; Parkinson diseases; dimentia; AIDS related dementia;

25 Alzheimer's diseases; Down's syndrome; Huntington's chorea; carcinoid syndrome; disorders related to immune enhancement or suppression; disorders caused by Helicobacter pylori or another spiral urease-positive gram-negative bacterium; sunburn; angiogenesis or diseases caused by angiogenesis; and the like.

30 It is furthermore expected that the object compound (I) and a pharmaceutically acceptable salt thereof of the present invention are useful for treating or preventing chronic obstructive pulmonary diseases, particularly chronic pulmonary emphysema; iritis; proliferative vitreoretinopathy;

psoriasis; inflammatory intestinal diseases, particularly Crohn's diseases; hepatitis; superficial pain on congelation, burn, herpes zoster or diabetic neuropathy; telalgia attended to hyperlipidemia; postoperative neuroma, particularly of mastectomy; vulvar vestibulitis; hemodialysis-associated itching; lichen planus; laryngopharyngitis; bronchiectasis; coniosis; whooping cough; pulmonary tuberculosis; cystic fibrosis; emesis (e.g., nausea, retching, vomiting, acute emesis, delayed emesis, anticipatory emesis, past operative nausea and vomiting (PONV), acute and/or delayed emesis induced by drugs such as cancer chemotherapeutic agents, etc.); mental diseases, particularly anxiety, depression, dysthymic disorders and schizophrenia; demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis; attenuation of morphine withdrawal; oedema, such as oedema caused by thermal injury; small cell carcinomas, particularly small cell lung cancer (SCLC); hypersensitivity disorders such as poison ivy; fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis; reflex sympathetic dystrophy such as shoulder/hand syndrome; addiction disorders such as alcoholism; stress related somatic disorders; rheumatic diseases such as fibrositis; and the like.

Furthermore, the object compound (I) and a pharmaceutically acceptable salt thereof of the present invention are Central Nervous System (CNS) penetrant.

For therapeutic purpose, the compound (I) and a pharmaceutically acceptable salt thereof of the present invention can be used in a form of pharmaceutical preparation containing one of said compound, as an active ingredient, in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient suitable for oral, parenteral, external including topical, enteral, intravenous, intramuscular, inhalant, nasal, intraarticular, intraspinal, transtracheal or transocular administration.

The pharmaceutical preparations may be solid, semi-solid or solutions such as capsules, tablets, pellets, dragees, powders, granules, suppositories, ointments, creams, lotions, inhalants, injections, cataplasms, gels, tapes, eye drops, solution, syrups, aerosols, suspension, emulsion, or the like. If desired, there may be included in these preparations, auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and other commonly used additives.

While the dosage of the compound (I) will vary depending upon the age and condition of a patient, an average single dose of about 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg of the compound (I) may be effective for treating Tachykinin-mediated diseases such as asthma and the like. In general, amounts between 0.1 mg/body and about 1,000 mg/body may be administered per day.

In order to show the utility of the object compound (I) and a pharmaceutically acceptable salt thereof, the pharmacological test data of some representative compounds of the present invention is shown in the following.

A. Evaluation of NK₁ antagonist transport efficiency to the central nervous system using a h-NK₁ receptor binding assay

[1] Test Method

(1) Administration of test compound and extraction of the compound from brain

Male SD rats were given an i.v. injection of a solution containing a test compound (1 mg/kg). 5 Min later the animals were anesthetized by ether, bled and perfused through the aorta asscendens with 20 ml of saline. The brain was rapidly removed, weighed and homogenized in 4 vol. ice-cold

distilled water by using Polytoron (KINEMATICA). To extract the test compound, 500 μ l of the homogenate, 100 μ l of methanol, 500 μ l of 0.1 N NaOH and 4 ml of ethyl acetate were mixed by shaking for 10 min at room temperature. The organic phase (2.5 ml) was recovered by centrifugation at 3,000 rpm for 10 min, dried and dissolved in dimethyl sulfoxide.

(2) h-NK₁ receptor binding assay

10 (a) Crude CHO cell membrane preparation

CHO cells permanently expressing h-NK₁ receptors were harvested and homogenized with a Dounce homogenizer at 4°C in a buffer (0.25 M sucrose, 25 mM Tris-HCl (pH 7.4), 10 mM MgCl₂, 1 mM EDTA, 5 μ g/ml p-APMSF). The homogenate was centrifuged (500 x g, 10 min), and the pellet was resuspended in the same buffer, homogenized, and centrifuged. The two supernatants were combined and centrifuged (100,000 x g, 1 hour). The crude cell membranes thus isolated were resuspended in a buffer (25 mM Tris-HCl (pH 7.4), 10 mM MgCl₂, 1 mM EDTA, 5 μ g/ml p-APMSF) and stored at -80° until use.

25 (b) ¹²⁵I-BH-Substance P binding to the prepared membrane

Cell membranes (6 μ g/ml) were incubated with ¹²⁵I-BH-Substance P (0.1 nM) with or without the extracted compounds in 0.25 ml of a medium (50 mM Tris-HCl (pH 7.4), 5 mM MnCl₂, 20 μ g/ml chymostatin, 40 μ g/ml bacitracin, 4 μ g/ml leupeptin, 5 μ g/ml p-APMSF, 200 μ g/ml BSA) at 22°C for 90 min. At the end of the incubation period, the contents were quickly filtered through a Blue Mat 11740 filter (pretreated with 0.1% polyethylenimine for 3 hours prior to use) by using SKATRON Cell Harvester. The filter was then washed with a washing buffer (50 mM Tris-HCl (pH 7.4), 5 mM MnCl₂). The

radioactivity was counted by using an auto gamma counter (Packard RIASTAR 5420A). All data presented are specific binding defined as that displaceable by 3 μ M unlabeled Substance P.

5

[II] Test Result

All of the following Test Compounds showed more than 80% inhibition rate of 125 I-BH-Substance P binding to h-NK₁ receptors at the dose of 1 mg/kg.

10

Test Compounds : The object compounds of the
Examples 4-(1), 4-(2), 7 and 8

15

B. Emesis in the dog

[I] Test Method

20

25

Individually housed adult female dogs (8 to 15 kg) were given an i.v. injection of a solution containing a test compound. 5 Min later the emetic responses (retching and vomiting) were induced by administration of subcutaneous apomorphine (0.1 mg/0.5 ml/kg) and observed for the next 60 min. The timing and number of retches and vomits observed were recorded for each animal. An individual animal was tested with at least 10 days between experiments.

[II] Test Result

30

The following Test Compound showed 100% inhibition rate of emesis in the dog at the dose of 0.32 mg/kg.

Test compound : The object compound of the
Example 4-(1)

35

The following Preparations and Examples are given for the purpose of illustrating this invention.

Preparation 1

- 5 (2-Methoxyethoxy)methyl chloride (4.87 ml) was added to a solution of 3-hydroxy-4-methylbenzoic acid (2.16 g) and N,N-diisopropylethylamine (9.2 ml) in 1,2-dichloroethane (40 ml) at room temperature. The mixture was stirred under reflux for 24 hours. After removal of the solvent by
- 10 evaporation, the residue was partitioned between aqueous diluted hydrochloric acid solution and ethyl acetate. The organic layer was separated and washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The crude oil was purified by column chromatography on silica gel
- 15 using mixed solvents of hexane and ethyl acetate (3:1). The fractions containing the objective compound were collected and evaporated under reduced pressure to give (2-methoxyethoxy)methyl 3-[(2-methoxyethoxy)methoxy]-4-methylbenzoate (4.82 g) as an oil.
- 20 IR (Neat) : 1725, 1595 cm^{-1}
NMR (CDCl_3 , δ) : 2.29 (3H, s), 3.37 (3H, s), 3.39 (3H, s), 3.54-3.90 (8H, m), 5.35 (2H, s), 5.60 (2H, s), 7.21 (1H, d, $J=8.0\text{Hz}$), 7.65 (1H, dd, $J=1.6$ and 8.0Hz), 7.74 (1H, d, $J=1.4\text{Hz}$)
- 25 MASS (API-ES) : 351 ($\text{M}+\text{Na}$)⁺

Preparation 2

- Lithium aluminum hydride (0.35 g) was added by small portions over 12 minutes to an ice-cooled solution of (2-methoxyethoxy)methyl 3-[(2-methoxyethoxy)methoxy]-4-
- 30 methylbenzoate (3.5 g) in tetrahydrofuran (20 ml) below 5°C under nitrogen atmosphere. After the mixture was stirred at the same temperature for 30 minutes, 2N sodium hydroxide (0.5 ml) was added to the mixture. After the mixture was stirred
- 35 for 30 minutes, the insoluble materials were removed by

filtration and washed with tetrahydrofuran. The filtrate and the washing were combined, and evaporated under reduced pressure. The residue was dissolved into ethyl acetate, and manganese(IV) oxide (3.5 g) was added to the solution. After
5 being stirred under reflux for 2 hours, the reaction mixture was filtered through Celite® and the insoluble mass was washed with ethyl acetate. The filtrate and the washing were combined and evaporated under reduced pressure. The resulting residue was purified by column chromatography on
10 silica gel using mixed solvents of hexane and ethyl acetate (10:1). The fractions containing the objective compound were collected and evaporated under reduced pressure to give 3-[(2-methoxyethoxy)methoxy]-4-methylbenzaldehyde (1.7 g) as an oil.

15 IR (Neat) : 1687, 1407 cm^{-1}

NMR (CDCl_3 , δ) : 2.31 (3H, s), 3.38 (3H, s), 3.55-3.60 (2H, m), 3.82-3.87 (2H, m), 5.37 (2H, s), 7.30 (1H, d, $J=7.7\text{Hz}$), 7.44 (1H, dd, $J=1.4$ and 7.7Hz), 7.58 (1H, d, $J=1.4\text{Hz}$), 9.92 (1H, s)

20 MASS (API-ES) : 279 ($\text{M}+\text{Na}+\text{MeOH}$)⁺, 247 ($\text{M}+\text{Na}$)⁺

Preparation 3

To a stirred mixture of 3-[(2-methoxyethoxy)methoxy]-4-methylbenzaldehyde (1.70 g) and 1,4-diacetyl-2,5-
25 piperazinedione (1.6 g) in a mixture of N,N-dimethylformamide (17 ml) and tert-butanol (17 ml) was added potassium tert-butoxide (900 mg) at 5°C. The mixture was stirred for 24 hours at room temperature and then poured into water (300 ml). The aqueous mixture was adjusted to pH 4-5 with aqueous
30 diluted hydrochloric acid solution and extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate and evaporated under reduced pressure. The resulting residue was purified by column chromatography on silica gel using mixed solvents of toluene and ethyl acetate
35 (3:1). The fractions containing the objective compound were

collected and evaporated under reduced pressure to give 1-acetyl-3-[3-[(2-methoxyethoxy)methoxy]-4-methylphenyl]-methylene-2,5-piperazinedione (2.05 g) as a powder.

IR (KBr) : 3208, 1700, 1627, 1598, 1455, 1375 cm^{-1}

5 NMR (CDCl_3 , δ) : 2.26 (3H, s), 2.65 (3H, s), 3.27 (3H, s), 3.58-3.62 (2H, m), 3.81-3.86 (2H, m), 4.49 (2H, s), 5.32 (2H, s), 6.94 (1H, dd, $J=1.5$ and 7.8Hz), 7.15 (1H, d, $J=7.8\text{Hz}$), 7.23 (1H, d, $J=1.5\text{Hz}$), 7.27 (1H, s), 8.34 (1H, br s)

10 MASS (API-ES) : 417 ($\text{M}+\text{MeOH}+\text{Na}$)⁺

Preparation 4

A solution of 1-acetyl-3-[[3-[(2-methoxyethoxy)methoxy]-4-methylphenyl]methylene]-2,5-piperazinedione (2.0 g) in 15 tetrahydrofuran (20 ml) was hydrogenated over 10% palladium-carbon (50% wet, 0.2 g) at room temperature under atmospheric pressure for 3 hours. After removal of the catalyst by filtration, the filtrate was concentrated under reduced pressure. The resulting residue was dissolved into 20 tetrahydrofuran (30 ml) and thereto was added hydrazine monohydrate (1.5 ml). After being stirred for 1 hour at room temperature, the mixture was concentrated under reduced pressure. The residue was triturated with isopropyl alcohol and the resulting solid was collected by filtration to give 25 3-[3-[(2-methoxyethoxy)methoxy]-4-methylbenzyl]-2,5-piperazinedione (1.75 g).

IR (KBr) : 3183, 3060, 1675, 1454 cm^{-1}

30 NMR (CDCl_3 , δ) : 2.21 (3H, s), 2.95-4.00 (8H, m), 3.36 (3H, s), 4.20-4.27 (1H, m), 5.19 (1H, d, $J=7.0\text{Hz}$), 5.38 (1H, d, $J=7.0\text{Hz}$), 6.50 (1H, br s), 6.72 (1H, br s), 6.75 (1H, dd, $J=1.4$ and 7.9Hz), 6.97 (1H, d, $J=1.4\text{Hz}$), 7.08 (1H, d, $J=7.9\text{Hz}$)

MASS (APCI) : 323 ($\text{M}+\text{H}$)⁺, 247, 235

Preparation 5

Lithium aluminum hydride (0.62 mg) was added to an ice-cooled solution of 3-[3-[(2-methoxyethoxy)methoxy]-4-methyl]-benzyl-2,5-piperazinedione (1.7 g) in tetrahydrofuran (17 ml) below 5°C under nitrogen atmosphere. The mixture was stirred under reflux for 3.5 hours. After the mixture was cooled below 5°C, 2N sodium hydroxide was added to the mixture. After the mixture was stirred for 30 minutes at the same temperature, the insoluble materials were removed by filtration and washed with tetrahydrofuran. The filtrate and the washing were combined and evaporated under reduced pressure. The residue was dissolved into ethyl acetate, and the solution was dried over sodium sulfate and evaporated under reduced pressure to give 2-[3-[(2-methoxyethoxy)-methoxy]-4-methylbenzyl]piperazine (1.27 g) as an oil.

A solution of benzyloxycarbonyl chloride (0.75 g) in dichloromethane (1 ml) was added dropwise over 5 minutes to an ice-cooled solution of 2-[3-[(2-methoxyethoxy)methoxy]-4-methylbenzyl]piperazine (1.27 g) obtained by above procedure and triethylamine (2.2 ml) in dichloromethane (10 ml) below 5°C. After the mixture was stirred for 30 minutes at the same temperature, a solution of 3,5-bis(trifluoromethyl)-benzoyl chloride (0.93 ml) in dichloromethane (1.0 ml) was added dropwise to the mixture over 10 minutes below 5°C. After being stirred for 30 minutes at the same temperature, the reaction mixture was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using mixed solvents of toluene and ethyl acetate (5:1). The fractions containing the objective compound were collected and evaporated under reduced pressure to give 1-[3,5-bis(trifluoromethyl)benzoyl]-4-(benzyloxycarbonyl)-2-[3-[(2-methoxyethoxy)methoxy]-4-methylbenzyl]piperazine (1.61 g) as an oil.

IR (Neat) : 2879, 1700, 1645 cm^{-1}

NMR (CDCl_3 , δ) : 2.19 (3H, s), 3.35 (3H, s), 2.40-5.40

(17H, m), 6.40-8.10 (10H, m), 7.82 (1H, br s)
MASS (APCI) : 669 (M+H)⁺

Preparation 6

5 A solution of 1-[3,5-bis(trifluoromethyl)benzoyl]-4-(benzyloxycarbonyl)-2-[3-[(2-methoxyethoxy)methoxy]-4-methylbenzyl]piperazine (1.6 g) in methanol (20 ml) was hydrogenated over 10% palladium-carbon (50% wet, 0.2 g) at room temperature under atmospheric pressure for 4 hours.
10 After removal of the catalyst by filtration, the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using mixed solvents of dichloromethane and methanol (40:1). The fractions containing the objective compound were collected
15 and evaporated under reduced pressure to give 1-[3,5-bis(trifluoromethyl)benzoyl]-2-[3-[(2-methoxyethoxy)methoxy]-4-methylbenzyl]piperazine (0.89 g) as an oil.

IR (Neat) : 1732, 1714, 1705, 1647, 1431 cm⁻¹

NMR (CDCl₃, δ) : 2.20 (3H, s), 2.50-5.20 (16H, m), 3.00
20 (3H, s), 6.40-7.40 (5H, m), 7.80 (1H, s)

MASS (API-ES) : 557 (M+Na)⁺, 535 (M+H)⁺

Preparation 7

25 To a mixed solution of (3R)-3-methoxymethylmorpholine hydrochloride (4.71 g) and triethylamine (4.11 ml) in methanol (110 ml) was added 5.8M ethylene oxide (22 ml) in toluene solution at room temperature. After the reaction mixture was stirred at the same temperature for two days, it was evaporated under reduced pressure. The residue was
30 purified by column chromatography on silica gel using mixed solvents of dichloromethane and methanol (20:1). The fractions containing the objective compound were collected and evaporated under reduced pressure to give 2-[(3R)-3-methoxymethylmorpholino]ethanol (4.67 g) as an oil.

35 IR (Neat) : 3433, 2860, 1454, 1119, 1055 cm⁻¹

NMR (CDCl_3 , δ) : 2.38-3.05 (5H, m), 3.33 (3H, s),
3.40-3.80 (8H, m)
MASS (APCI) : 176 ($\text{M}+\text{H}$)⁺

5 Preparation 8

The following compounds were obtained according to a similar manner to that of Preparation 8.

(1) 2-[cis-2,6-Dimethylmorpholino]ethanol

10 IR (Neat) : 3431, 3402, 1456, 1373, 1325, 1146 cm^{-1}
NMR (CDCl_3 , δ) : 1.17 (6H, d, $J=6.3\text{Hz}$), 1.84 (2H, dd,
 $J=10.2$ and 11.4Hz), 2.52 (2H, t, $J=5.5\text{Hz}$), 2.71-
2.78 (2H, m), 3.65 (2H, t, $J=5.6\text{Hz}$), 3.49-3.76 (2H,
m)
15 MASS (APCI) : 160 ($\text{M}+\text{H}$)⁺

(2) 2-[(2S,5S)-2-Methoxymethyl-5-methylmorpholino]ethanol

IR (Neat) : 3433, 3400, 1456, 1379, 1327, 1086,
1051 cm^{-1}
20 NMR (CDCl_3 , δ) : 1.19 (3H, d, $J=6.3\text{Hz}$), 1.88 (1H, d,
 $J=10.8\text{Hz}$), 1.96 (1H, t, $J=10.5\text{Hz}$), 2.54 (2H, t,
 $J=5.5\text{Hz}$), 2.72-2.83 (2H, m), 3.38 (3H, s), 3.36-
3.45 (2H, m), 3.63 (2H, t, $J=5.2\text{Hz}$), 3.60-3.90 (2H,
m)
25 MASS (APCI) : 190 ($\text{M}+\text{H}$)⁺

(3) 2-[(2S)-2-Methoxymethylmorpholino]ethanol

IR (Neat) : 3435, 1456, 1354, 1302 cm^{-1}
NMR (CDCl_3 , δ) : 2.06 (1H, t, $J=10.7\text{Hz}$), 2.27 (1H, td,
30 $J=10.7$ and 3.3Hz), 2.53-2.58 (2H, m), 2.68-2.84
(2H, m), 3.38 (3H, s), 3.38-3.44 (2H, m), 3.61-3.75
(4H, m), 3.89-3.98 (1H, m)
MASS (API-ES) : 176 ($\text{M}+\text{H}$)⁺, 198 ($\text{M}+\text{Na}$)⁺

35 Preparation 9

To an ice-cooled solution of 2-[(3R)-3-methoxymethylmorpholino]ethanol (505 mg) in toluene (2.5 ml) was added dropwise a solution of thionyl chloride (429 mg) in toluene (1.5 ml) below 5°C under nitrogen atmosphere. The mixture was stirred at 70°C for 1.5 hours. After the mixture was cooled at room temperature, ethyl acetate was added to the mixture, and resulting suspension was evaporated under reduced pressure. Diisopropyl ether was added to the residue, and after the mixture was stirred at room temperature for 15 minutes, the resulting precipitates were collected by filtration, washed with diisopropyl ether and dried at 40°C under reduced pressure to give (3R)-4-(2-chloroethyl)-3-methoxymethylmorpholine hydrochloride (620 mg) as a light yellowish powder.

mp : 162-163°C

IR (KBr) : 2945, 1140, 1109, 1084 cm^{-1}

NMR (DMSO- d_6 , δ) : 3.31 (3H, s), 3.10-4.10 (13H, m)

MASS (APCI) : 194 (M+H)⁺ (free)

Preparation 10

The following compounds were obtained according to a similar manner to that of Preparation 9.

(1) cis-2,6-Dimethyl-4-(2-chloroethyl)morpholine hydrochloride

IR (KBr) : 1513, 1458, 1394, 1336, 1143 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.12 (6H, d, J=6.3Hz), 2.60-2.80 (2H, m), 3.44-3.50 (4H, m), 3.95-4.10 (4H, m)

MASS (APCI) : 178 (M+H)⁺ (free)

(2) (2S,5S)-4-(2-Chloroethyl)-2-methoxymethyl-5-methylmorpholine hydrochloride

IR (KBr) : 2613, 1456, 1390, 1124, 1082 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.13 (3H, d, J=6.3Hz), 2.50-3.00

(3H, m), 3.27 (3H, s), 3.34-3.51 (7H, m), 4.03-4.10

(4H, m)

MASS (APCI) : 208 (M+H)⁺ (free)

(3) (2S)-4-(2-Chloroethyl)-2-methoxymethylmorpholine
hydrochloride

NMR (DMSO-d₆, δ) : 3.00 (2H, m), 3.27 (3H, s), 3.47
(4H, m), 3.75-4.12 (7H, m), 11.91 (1H, m)

MASS (APCI) : 194 (M+H)⁺ (free)

Preparation 11

Sodium triacetoxymethylborohydride (36.7 g) was added portionwisely to a mixture of (2S)-2-amino-1-propanol (10.0 g) and benzaldehyde (13.53 ml) in a mixture of dichloromethane (140 ml) and acetic acid (8.38 ml) at 0°C and the whole was stirred at room temperature overnight. The mixture was washed successively with 2N sodium hydroxide and brine, and dried over sodium sulfate. The solution was evaporated under reduced pressure and the resulting residue was purified by column chromatography on silica gel using a mixed solvent of dichloromethane and methanol (30:1). The fractions containing the objective compound were collected and evaporated under reduced pressure to give (2S)-2-benzylamino-1-propanol (15.96 g).

IR (KBr) : 2843, 1496, 1454, 1377, 1340, 1065 cm⁻¹

NMR (CDCl₃, δ) : 1.10 (3H, d, J=6.4Hz), 2.77-2.93 (1H, m), 3.28 (1H, dd, J=10.6 and 6.9Hz), 3.61 (1H, dd, J=10.6 and 4.0Hz), 3.75, 3.87 (2H, ABq, J=13Hz), 7.21-7.34 (5H, m)

MASS (API-ES) : 166 (M+H)⁺

Preparation 12

(s)-(+)-Methyl glycidyl ether (8.25 ml) was added dropwise to a solution of (2S)-2-benzylamino-1-propanol (7.6 g) in methanol (7.6 ml) at room temperature. After being stirred at 40-50° for 24 hours, the solution was concentrated

under reduced pressure. The residue was purified by column chromatography on silica gel using mixed solvents of dichloromethane and methanol (30:1). The fractions containing the objective compound were collected and
5 evaporated under reduced pressure to give (2S)-2-[N-benzyl-N-[(2S)-2-hydroxy-3-methoxypropyl]amino]-1-propanol (10.4 g) as an oil.

IR (Neat) : 3400, 2929, 1452, 1414, 1373, 1329 cm^{-1}

10 NMR (CDCl_3 , δ) : 0.96 (3H, d, $J=6.7\text{Hz}$), 2.50-2.60 (1H, m), 2.57 (1H, dd, $J=13.4$ and 6.2Hz), 2.67 (1H, dd, $J=13.4$ and 6.5Hz), 2.95-3.10 (1H, m), 3.21-3.52 (4H, m), 3.30 (3H, s), 3.49 (1H, d, $J=13.6\text{Hz}$), 3.71-3.75 (1H, m), 3.83 (1H, d, $J=13.6\text{Hz}$), 7.21-7.37 (5H, m)

15 MASS (APCI) : 254 ($\text{M}+\text{H}$)⁺

Preparation 13

Triphenylphosphine (10.09 g) was added to a solution of (2S)-2-[N-benzyl-N-[(2S)-2-hydroxy-3-methoxypropyl]amino]-1-propanol (8.86 g) in tetrachloromethane (4.06 ml) at room
20 temperature. After being stirred at room temperature for 2 days, the solution was concentrated under reduced pressure. The residue was triturated with diisopropyl ether (200 ml) three times, and the soluble portions were separated by
25 decantation and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using mixed solvents of dichloromethane and methanol (40:1). The fractions containing the objective compound were collected and evaporated under reduced pressure to give (2S)-
30 1-[N-benzyl-N-[(1S)-2-chloro-1-methylethyl]amino]-3-methoxy-2-propanol (4.90 g) as an oil.

IR (Neat) : 3463, 1452, 1362 cm^{-1}

35 NMR (CDCl_3 , δ) : 1.43 (3H, d, $J=6.6\text{Hz}$), 2.53-2.82 (4H, m), 3.30-3.39 (2H, m), 3.36 (3H, s), 3.59 (1H, d, $J=13.6\text{Hz}$), 3.83 (1H, d, $J=13.6\text{Hz}$), 3.79-3.87 (1H,

m), 4.01-4.09 (1H, m), 7.21-7.33 (5H, m)
MASS (APCI) : 272 (M+H)⁺

Preparation 14

5 A solution of (2S)-1-[N-benzyl-N-[(1S)-2-chloro-1-methylethyl]amino]-3-methoxy-2-propanol (1.90 g) in N,N-dimethylformamide (10 ml) was added to an ice-cooled suspension of sodium hydride (0.45 g, 60% in mineral oil) in N,N-dimethylformamide (10 ml) at 0°C. After being stirred
10 for 1 hour at the same temperature, the mixture was poured into ice-water and extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using mixed solvents
15 of hexane and ethyl acetate (10:1). The fractions containing the objective compound were collected and evaporated under reduced pressure to give (2S,5S)-4-benzyl-2-methoxymethyl-5-methylmorpholine (0.86 g) as an oil.

IR (Neat) : 2875, 1452, 1362, 1325, 1130, 1082 cm⁻¹

20 NMR (CDCl₃, δ) : 1.15 (3H, d, J=6.3Hz), 1.73-1.93 (2H, m), 2.68-2.77 (2H, m), 3.35 (3H, s), 3.49 (2H, s), 3.31-3.49 (2H, m), 3.68-3.81 (2H, m), 7.25-7.32 (5H, m)

MASS (APCI) : 236 (M+H)⁺

Preparation 15

A solution of (2S,5S)-4-benzyl-2-methoxymethyl-5-methylmorpholine (0.86 g) in a mixture of concentrated hydrochloric acid (0.31 ml) and methanol (8.6 ml) was
30 hydrogenated over 10% palladium-carbon (50% wet, 0.2 g) at room temperature under atmospheric pressure for 3 hours. After removal of the catalyst by filtration through Celite®, the filtrate was concentrated under reduced pressure to give (2S,5S)-2-methoxymethyl-5-methylmorpholine hydrochloride
35 (0.71 g) as an oil.

IR (Neat) : 3433, 3402, 2939, 1597, 1456, 1392, 1331,
1107 cm^{-1}

NMR (DMSO-d_6 , δ) : 1.12 (3H, d, $J=6.3\text{Hz}$), 2.49-2.75
(2H, m), 3.13-3.19 (2H, m), 3.27 (3H, s), 3.38 (2H,
5 d, $J=4.8\text{Hz}$), 3.80-4.00 (2H, m)

MASS (APCI) : 146 ($\text{M}+\text{H}$)⁺ (free)

Preparation 16

N-Acetyl-3-methoxy-4-methyl-DL-phenylalanine (7.28 g)
10 was dissolved into a mixture of water (36.5 ml) and 1N sodium
hydroxide solution (29 ml). Cobalt(II) chloride hexahydrate
(36.5 mg) and acylase (Acylase Amano, 365 mg) were added to
the solution and the mixture was stirred at 37°C for 15.5
hours with controlling the pH of the reaction mixture to 7.5
15 with 1N sodium hydroxide solution. The insoluble material
was removed by filtration and the pH of the filtrate was made
to 3 with 6N hydrochloric acid, extracted with ethyl acetate,
washed with water, dried over sodium sulfate, and evaporated
in vacuo to give crude N-acetyl-3-methoxy-4-methyl-D-
20 phenylalanine (3.17 g). The crude product was again
subjected to the acylase reaction (cobalt(II) chloride
hexahydrate 15.2 mg, acylase 152 mg, 37°C, pH 7.5, 20 hours)
to give pure N-acetyl-3-methoxy-4-methyl-D-phenylalanine
(2.70 g) as a viscous oil.

25 $[\alpha]_D^{26.8}$: -36.16° ($C=0.424$, MeOH)

IR (Neat) : 3350, 1740, 1725 cm^{-1}

NMR (CDCl_3 , δ) : 1.99 (3H, s), 2.17 (3H, s), 3.00-3.25
(2H, m), 4.75-4.90 (1H, m), 6.00-7.10 (3H, m), 6.36
(2H, br s)

30 MASS (APCI) : 252 ($\text{M}+\text{H}$)⁺

Preparation 17

A mixture of N-acetyl-3-methoxy-4-methylphenyl-D-alanine
(2.55 g) in a mixture of 6N hydrochloric acid (25.5 ml) and
35 toluene (18 ml) was stirred under reflux for 4 hours. After

being cooled to room temperature, the aqueous layer was separated and the organic layer was washed with water (10 ml) twice. The aqueous layer and the washings were combined and evaporated under reduced pressure. The resulting crystals were collected by filtration and washed with ice-water to give 3-methoxy-4-methyl-D-phenylalanine hydrochloride (1.35 g) as colorless crystals. The filtrate was evaporated under reduced pressure to give crude 3-methoxy-4-methyl-D-phenylalanine hydrochloride (0.6 g).

mp : 207-211°C

$[\alpha]_D^{27.2}$: +20.2° (C=0.5, H₂O)

IR (KBr) : 1735, 1610, 1508 cm⁻¹

NMR (D₂O, δ) : 2.18 (3H, s), 3.17 (1H, dd, J=7.6 and 14.6Hz), 3.32 (1H, dd, J=6.0 and 14.6Hz), 3.85 (3H, s), 4.27 (1H, dd, J=6.0 and 7.0Hz), 6.85 (1H, d, J=7.3Hz), 6.91 (1H, s), 7.21 (1H, d, J=8.0Hz)

MASS (APCI) : 210 (M+H)⁺ (free)

Preparation 18

Thionyl chloride (0.7 ml) was added dropwise to a solution of 3-methoxy-4-methyl-D-phenylalanine hydrochloride (1.75 g) in methanol (8 ml) over 10 minutes at room temperature. The whole was stirred at 40-50°C for 2 hours and then an additional thionyl chloride (0.7 ml) was added to the mixture. The whole mixture was stirred for further 1 hour and evaporated under reduced pressure. The resulting solid was triturated with diisopropyl ether and collected by filtration to give colorless crystals of 3-methoxy-4-methyl-D-phenylalanine methyl ester hydrochloride (1.70 g).

mp : 196-197°C

$[\alpha]_D^{30}$: -4.60° (C=0.5, MeOH)

IR (Nujol) : 3400, 1741, 1583, 1465, 1446, 1249 cm⁻¹

NMR (D₂O, δ) : 2.19 (3H, s), 3.21 (1H, dd, J=7.4 and 14.5Hz), 3.32 (1H, dd, J=6.0 and 14.5Hz), 3.85 (6H, s), 4.43 (1H, dd, J=6.0 and 7.4Hz), 6.82 (1H, dd,

J=1.4 and 7.6Hz), 6.87 (1H, d, J=1.4Hz), 7.22 (1H, d, J=7.6Hz)

MASS (APCI) : 224 (M+H)⁺ (free), 207, 164

5 Preparation 19

Potassium carbonate (1.70 g) was added by small portions with ice-cooling to a mixture of 3-methoxy-4-methyl-D-phenylalanine methyl ester hydrochloride (1.60 g) in mixed solvents of dichloromethane (7 ml) and water (9 ml).

10 Chloroacetyl chloride (0.66 ml) was added to the mixture below 5°C over 15 minutes and then the whole was stirred for 30 minutes. The organic layer was separated, washed with brine, dried over magnesium sulfate and evaporated under reduced pressure to give an oil of (2R)-2-[N-(chloroacetyl)-
15 amino]-3-(3-methoxy-4-methylphenyl)propionic acid methyl ester.

IR (Neat) : 3305, 1737, 1643, 1583 cm⁻¹

Preparation 20

20 Benzylamine (1.65 g) and potassium carbonate (1.28 g) were added successively to a solution of (2R)-2-[N-(chloroacetyl)amino]-3-(3-methoxy-4-methylphenyl)propionic acid methyl ester (1.85 g) in N,N-dimethylformamide (15 ml) at 20°C. After being stirred at 35°C for 1.5 hours, the
25 mixture was poured into a mixture of ice-water (20 ml) and dichloromethane (20 ml). After the mixture was adjusted to pH 9 with diluted aqueous hydrochloric acid under stirring, the organic layer was separated, washed with brine (20 ml), dried over magnesium sulfate and evaporated under reduced
30 pressure to give an oil of (2R)-2-[N-(benzylacetyl)amino]-3-(3-methoxy-4-methylphenyl)propionic acid methyl ester. A solution of (2R)-2-[N-(benzylacetyl)amino]-3-(3-methoxy-4-methylphenyl)propionic acid methyl ester obtained by above procedure and acetic acid (0.18 ml) in isopropyl alcohol (10
35 ml) was stirred for 12 hours under reflux.

After the mixture was cooled to room temperature, isopropyl ether was added to the mixture. The resulting precipitates were collected by filtration and washed with isopropyl ether to give colorless crystals of (3R)-1-benzyl-3-(3-methoxy-4-methylphenyl)piperazine-2,5-dione (1.45 g).

mp : 205-209°C

$[\alpha]_D^{30}$: +11.12° (C=0.4, DMF)

IR (KBr) : 3237, 1677, 1656, 1465, 1446, 1442 cm⁻¹

NMR (DMSO-d₆, δ) : 2.08 (3H, s), 2.76 (1H, d, J=17.2Hz), 2.87 (1H, dd, J=4.8 and 13.4Hz), 3.11 (1H, dd, J=4.8 and 13.4Hz), 3.46 (1H, d, J=17.2Hz), 3.69 (3H, s), 4.25 (1H, d, J=14.6Hz), 4.20-4.30 (1H, m), 4.52 (1H, d, J=14.6Hz), 6.54 (1H, dd, J=1.4 and 7.4Hz), 6.69 (1H, d, J=1.4Hz), 6.87 (1H, d, J=7.4Hz), 7.04-7.11 (2H, m), 7.24-7.30 (3H, m), 8.33 (1H, d, J=2.2Hz)

MASS (APCI) : 339 (M+H)⁺

Preparation 21

Lithium aluminum hydride (0.378 g) was added to an ice-cooled suspension of (3R)-1-benzyl-3-(3-methoxy-4-methylphenyl)-2,5-piperazinedione (1.35 g) in tetrahydrofuran (22 ml) below 5°C under nitrogen atmosphere. The mixture was stirred under reflux for 3 hours. After the mixture was cooled below 5°C, 2N sodium hydroxide was added to the mixture. After the mixture was stirred for 30 minutes, the insoluble materials were removed by filtration and washed with tetrahydrofuran. The filtrate and the washing were combined and evaporated under reduced pressure to give (3R)-1-benzyl-3-(3-methoxy-4-methylphenyl)piperazine as an oil. A solution of 3,5-bis(trifluoromethyl)benzoyl chloride (0.80 ml) in dichloromethane (1 ml) was added dropwise over 5 minutes to an ice-cooled solution of (3R)-1-benzyl-3-(3-methoxy-4-methylphenyl)piperazine obtained by above procedure and triethylamine (0.84 ml) in dichloromethane (10 ml) below

5°C. After being stirred for 30 minutes at the same temperature, the reaction mixture was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using mixed solvents of hexane and ethyl acetate (4:1). The fractions containing the objective compound were collected and evaporated under reduced pressure to give (2R)-4-benzyl-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3-methoxy-4-methylbenzyl)piperazine (1.92 g) as an oil.

IR (Neat) : 2950, 2850, 1640, 1590, 1515 cm^{-1}

NMR (CDCl_3 , δ) : 2.16 (3H, s), 2.00-5.20 (14H, m), 6.25-6.32 (1H, m), 6.70-6.90 (2H, m), 7.20-7.44 (7H, m), 7.80 (1H, br s)

MASS (APCI) : 551 ($\text{M}+\text{H}$)⁺, 573 ($\text{M}+\text{Na}$)⁺

Preparation 22

A solution of boron tribromide in dichloromethane (1M solution, 3.7 ml) was added dropwise over 20 minutes to an ice-cooled solution of (2R)-4-benzyl-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3-methoxy-4-methylbenzyl)piperazine (0.68 g) in dichloromethane (5 ml). After being stirred at the same temperature for 2 hours, followed by further stirring at room temperature for 12 hours, the mixture was poured into aqueous saturated sodium hydrogen carbonate solution. The organic layer was separated, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using mixed solvents of hexane and ethyl acetate (4:1). The fractions containing the objective compound were collected and evaporated under reduced pressure to give (2R)-4-benzyl-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3-hydroxy-4-methylbenzyl)piperazine (0.56 g) as a red foam.

IR (Neat) : 1630, 1430 cm^{-1}

NMR (CDCl_3 , δ) : 2.00-5.20 (14H, m), 5.61 (1H, br s), 6.20-6.25 (1H, m), 6.60-7.70 (2H, m), 7.20-7.60

(7H, m), 7.80-7.85 (1H, m)

MASS (API-ES) : 519 (M-H₂O+H)⁺, 537 (M+H)⁺, 559 (M+Na)⁺

Preparation 23

5 Sodium hydride (60% in mineral oil, 18 mg) was added by
small portions to an ice-cooled solution of (2R)-4-benzyl-1-
[3,5-bis(trifluoromethyl)benzoyl]-2-(3-hydroxy-4-
methylbenzyl)piperazine (0.20 g) in N,N-dimethylformamide (2
ml) below 5°C under nitrogen atmosphere. After the mixture
10 was stirred for 5 minutes, (2-methoxyethoxy)methyl chloride
(0.064 ml) was added to the mixture. The whole was stirred
at room temperature for 2.5 hours, and thereto water was
added. The whole was extracted with ethyl acetate. The
extract was dried over magnesium sulfate and evaporated under
15 reduced pressure. The residue was purified by column
chromatography on silica gel using mixed solvents of hexane
and ethyl acetate (7:3). The fractions containing the
objective compound were collected and evaporated under
reduced pressure to give (2R)-4-benzyl-1-[3,5-
20 bis(trifluoromethyl)benzoyl]-2-[3-[(2-methoxyethoxy)methoxy]-
4-methylbenzyl]piperazine (0.21 g) as an oil.

IR (Neat) : 2950, 1645, 1435 cm⁻¹

NMR (CDCl₃, δ) : 2.19 (3H, s), 3.34 (3H, s), 2.00-5.20

(17H, m), 6.60-7.40 (10H, m), 7.70-7.80 (1H, m)

25 MASS (API-ES) : 625 (M+H)⁺, 647 (M+Na)⁺

Preparation 24

A mixture of (2R)-4-benzyl-1-[3,5-bis(trifluoromethyl)-
benzoyl]-2-[3-[(2-methoxyethoxy)methoxy]-4-methylbenzyl]-
30 piperazine (0.38 g) in methanol (6 ml) was hydrogenated over
20% palladium hydroxide-carbon (0.06 g) at room temperature
under atmospheric pressure for 8 hours. After removal of the
catalyst by filtration through Celite[®], the filtrate was
concentrated under reduced pressure. The residue was
35 purified by column chromatography on silica gel using mixed

solvents of dichloromethane and methanol (30:1). The fractions containing the objective compound were collected and evaporated under reduced pressure to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-[3-[(2-methoxyethoxy)methoxy]-4-methylbenzyl]piperazine (0.32 g) as an oil.

IR (KBr) : 3000-2700, 1629, 1513, 1444 cm^{-1}

NMR (CDCl_3 , δ) : 2.20 (3H, s), 2.50-5.30 (16H, m), 3.36 (3H, s), 6.40-7.50 (5H, m), 7.80 (1H, s)

MASS (API-ES) : 535 ($\text{M}+\text{H}$)⁺, 557 ($\text{M}+\text{Na}$)⁺

Example 1

To a solution of 1-[3,5-bis(trifluoromethyl)benzoyl]-2-[3-[(2-methoxyethoxy)methoxy]-4-methylbenzyl]piperazine (440 mg) in N,N-dimethylformamide (2.2 ml) were added (3R)-4-(2-chloroethyl)-3-methoxymethylmorpholine hydrochloride (289 mg), potassium carbonate (434 mg) and potassium iodide (149 mg) at room temperature. The whole was stirred at 73°C for 2 hours. After being cooled to room temperature, the mixture was poured into ice-water and the aqueous mixture was made alkaline with saturated aqueous sodium hydrogen carbonate solution. The resulting mixture was extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using mixed solvents of dichloromethane and methanol (40:1). The fractions containing the objective compound were collected and evaporated under reduced pressure to give 1-[3,5-bis(trifluoromethyl)benzoyl]-2-[3-[(2-methoxyethoxy)methoxy]-4-methylbenzyl]-4-[2-[(3R)-3-methoxymethylmorpholino]ethyl]piperazine (450 mg) as a light yellowish oil.

IR (Neat) : 2879, 1639, 1437, 1281, 1136, 1009 cm^{-1}

NMR (CDCl_3 , δ) : 2.20 (3H, s), 1.95-5.40 (34H, m), 6.40-8.10 (6H, m)

MASS (APCI) : 692 ($\text{M}+\text{H}$)⁺

Example 2

The following compounds were obtained according to a similar manner to that of Example 1.

- 5 (1) 1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[2-(cis-2,6-dimethylmorpholino)ethyl]-2-[3-[(2-methoxyethoxy)-methoxy]-4-methylbenzyl]piperazine
 IR (Neat) : 1680, 1643, 1508, 1435 cm^{-1}
 NMR (CDCl_3 , δ) : 1.17 (6H, d, $J=6.3\text{Hz}$), 1.78 (2H, t, $J=10.8\text{Hz}$), 2.20 (3H, br s), 2.20-5.30 (23H, m),
 10 3.36 (3H, s), 6.42-8.02 (6H, m)
 MASS (APCI) : 676 ($\text{M}+\text{H}$)⁺
- (2) 1-[3,5-Bis(trifluoromethyl)benzoyl]-2-[3-[(2-methoxyethoxy)methoxy]-4-methylbenzyl]-4-[2-[(2S,5S)-2-methoxymethyl-5-methylmorpholino]ethyl]piperazine
 15 IR (Neat) : 2933, 2881, 1643, 1439, 1281, 1086, 1012 cm^{-1}
 NMR (CDCl_3 , δ) : 1.18 (3H, d, $J=6.2\text{Hz}$), 1.78-1.96 (2H, m), 2.20 (3H, br s), 2.20-5.30 (25H, m), 3.37 (3H, s), 3.36 (3H, s), 6.66-7.80 (6H, m)
 20 MASS (API-ES) : 706.3 ($\text{M}+\text{H}$)⁺, 728.3 ($\text{M}+\text{Na}$)⁺

Example 3

- 25 1-[3,5-Bis(trifluoromethyl)benzoyl]-2-[3-[(2-methoxyethoxy)methoxy]-4-methylbenzyl]-4-[2-[(3R)-3-methoxymethylmorpholino]ethyl]piperazine (430 mg) was dissolved in methanol (10 ml) at room temperature, and methanesulfonic acid (0.215 ml) was added to the solution.
 30 After being stirred at the same temperature for 18 hours, the reaction mixture was concentrated until one third of original volume under reduced pressure, and poured into iced water. The aqueous mixture was made alkaline with 15% aqueous sodium hydroxide solution, and the resulting mixture was extracted
 35 with ethyl acetate. The extract was washed with brine, dried

over sodium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using mixed solvents of dichloromethane and methanol (30:1). The fractions containing the objective compound were collected and evaporated under reduced pressure, and the residue was treated with 4N hydrogen chloride in ethyl acetate solution to give 1-[3,5-bis(trifluoromethyl)benzoyl]-2-[3-hydroxy-4-methylbenzyl]-4-[2-[(3R)-3-methoxymethylmorpholino]ethyl]piperazine dihydrochloride (280 mg) as a colorless powder.

mp : 167-172°C

$[\alpha]_D^{28}$: -8.50° (C=0.20, MeOH)

IR (KBr) : 3400, 1645, 1429, 1282, 1184, 1138 cm⁻¹

NMR (DMSO-d₆, δ) : 2.08 (3H, s), 2.60-5.10 (25H, m), 6.18-7.10 (3H, m), 7.36-8.22 (3H, m), 9.25 (1H, br)

MASS (APCI) : 604 (M+H)⁺ (free)

Example 4

The following compounds were obtained according to a similar manner to that of Example 3.

(1) 1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[2-(cis-2,6-dimethylmorpholino)ethyl]-2-(3-hydroxy-4-methylbenzyl)piperazine dihydrochloride

mp : 188-200°C

$[\alpha]_D^{29}$: +0.70° (C=0.25, MeOH)

IR (KBr) : 3402, 1643, 1516, 1429 cm⁻¹

NMR (DMSO-d₆, δ) : 1.15 (6H, d, J=6.0Hz), 2.08 (3H, br s), 2.00-5.10 (19H, m), 6.19-8.21 (6H, m)

MASS (APCI) : 588 (M+H)⁺ (free)

(2) 1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(3-hydroxy-4-methylbenzyl)-4-[2-[(2S,5S)-2-methoxymethyl-5-methylmorpholino]ethyl]piperazine dihydrochloride

mp : 214-218°C

$[\alpha]_D^{29}$: +0.80° (C=0.25, MeOH)

IR (KBr) : 3433, 3398, 1645, 1516, 1429, 1371, 1281,
1182, 1140 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.16 (3H, d, J=6.0Hz), 2.08 (3H, br
s), 2.50-5.10 (21H, m), 3.27 (3H, s), 6.20-8.20
(6H, m), 9.00-9.20 (1H, m)

MASS (APCI) : 618 (M+H)⁺ (free)

(3) 1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(3-hydroxy-4-
methylbenzoyl)-4-[3-(3-pyridyl)-2-propynyl]piperazine

NMR (CDCl₃, δ) : 0.60-5.30 (14H, m), 5.77 (1H, br s),
6.20-8.90 (10H, m)

MASS (APCI) : 562 (M+H)⁺

Example 5

The following compounds were obtained according to a
similar manner to that of Example 1 and then a similar manner
to that of Example 3.

(1) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[2-[(2S)-2-
methoxymethylmorpholino]ethyl]-2-(3-hydroxy-4-
methylbenzyl)piperazine dihydrochloride

mp : 207-210°C

$[\alpha]_D^{26.2}$: -6.40° (C=0.4, MeOH)

IR (KBr) : 3300, 3000, 2700, 1644, 1428 cm^{-1}

NMR (DMSO- d_6 , δ) : 2.18 (3H, s), 2.20-5.20 (22H, m),
6.10-8.20 (6H, m), 9.00-9.40 (1H, br s), 11.00-
12.00 (2H, m)

MASS (APCI) : 604 (M+H)⁺ (free)

(2) 1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[2-[(2S)-2-
methoxymethylmorpholino]ethyl]-2-(3-hydroxy-4-
methylbenzyl)piperazine dihydrochloride

IR (KBr) : 1645, 1516, 1458, 1425, 1369 cm^{-1}

NMR (DMSO- d_6 , δ) : 2.08 (3H, br s), 3.28 (3H, br s),

2.40-5.10 (22H, m), 6.19-8.22 (6H, m)

MASS (APCI) : 604 (M+H)⁺ (free)

Example 6

5 A mixture of 1-[3,5-bis(trifluoromethyl)benzoyl]-2-[3-
[(2-methoxyethoxy)methoxy]-4-methylbenzyl]piperazine (0.4 g),
1-chloro-3-(3-pyridyl)-2-propyne hydrochloride (0.17 g),
potassium carbonate (0.52 g) and a trace of potassium iodide
in N,N-dimethylformamide (7 ml) was stirred for 4 hours at
10 80°C. After cooling, the solvent was removed by evaporation,
and ethyl acetate and aqueous sodium hydrogen carbonate
solution were added thereto. The organic layer was
separated, dried over magnesium sulfate, and evaporated under
reduced pressure. The residue was purified by column
15 chromatography on silica gel using ethyl acetate. The
fractions containing the objective compound were collected
and evaporated under reduced pressure to give 1-[3,5-
bis(trifluoromethyl)benzoyl]-2-[3-[(2-methoxyethoxy)methoxy]-
4-methylbenzyl]-4-[3-(3-pyridyl)-2-propynyl]piperazine (0.44
20 g) as an oil.

NMR (CDCl₃, δ) : 0.60-5.60 (23H, m), 6.30-8.90 (10H, m)

MASS (APCI) : 650 (M+H)⁺

Example 7

25 A solution of 1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3-
hydroxy-4-methylbenzyl)-4-[3-(3-pyridyl)-2-propynyl]-
piperazine (0.11 g) in methanol (10 ml) was treated with 4N
hydrogen chloride in ethyl acetate (1 ml) and the mixture was
evaporated under reduced pressure. The residue was
30 triturated with a mixture of dichloromethane and ethyl
acetate and the resulting powder was collected by filtration
to give 1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3-hydroxy-4-
methylbenzyl)-4-[3-(3-pyridyl)-2-propynyl]piperazine
dihydrochloride (0.07 g).

35 mp : 180-190°C

IR (KBr) : 1693, 1676, 1645, 1549, 1531, 1516, 1460,
1456, 1427, 1392, 1367, 1317, 1281, 1217, 1188,
1066 cm^{-1}

NMR (DMSO-d_6 , δ): 1.60-5.20 (14H, m), 6.10-9.00 (10H, m)

5 MASS (APCI) : 562 ($\text{M}+\text{H}$)⁺ (free)

Example 8

A solution of 1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3-hydroxy-4-methylbenzyl)-4-[3-(3-pyridyl)-2-propynyl]-
10 piperazine (0.16 g) in a mixed solvent of methanol (10 ml) and tetrahydrofuran (10 ml) was hydrogenated over 10% palladium-charcoal (20 mg) at room temperature for 1.5 hours. After removal of catalyst by filtration, the filtrate was concentrated under reduced pressure. The residue was
15 purified by column chromatography on silica gel using ethyl acetate as an eluent. The fractions containing the objective compound were collected and evaporated under reduced pressure and the resulting residue was treated with 4N hydrogen chloride in ethyl acetate to give 1-[3,5-
20 bis(trifluoromethyl)benzoyl]-2-(3-hydroxy-4-methylbenzyl)-4-[3-(3-pyridyl)propyl]piperazine dihydrochloride (0.17 g) as a colorless solid.

mp : 60-70°C

IR (KBr) : 1707, 1693, 1676, 1645, 1628, 1558, 1550,
25 1541, 1516, 1466, 1456, 1427, 1387, 1365, 1329,
1319, 1281, 1182, 1136, 1039 cm^{-1}

NMR (DMSO-d_6 , δ): 1.80-5.20 (18H, m), 6.00-9.00 (10H, m)

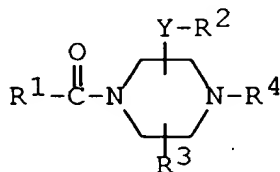
MASS (APCI) : 566 ($\text{M}+\text{H}$)⁺ (free)

30

35

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound of the formula :



wherein

Y is bond or lower alkylene,

R¹ is aryl which may be substituted with suitable substituent(s),

R² is aryl or indolyl, each of which may be substituted with suitable substituent(s),

R³ is hydrogen or lower alkyl,

R⁴ is (3-pyridyl)methyl;

(3-pyridyl)ethyl;

3-(3-pyridyl)propyl;

3-(3-pyridyl)propenyl;

3-(3-pyridyl)propynyl;

pyrazolylmethyl which may be substituted with hydroxy(lower)alkyl;

pyrazolyl(lower)alkyl which is substituted with lower alkyl,

(lower)alkoxy(lower)alkylmorpholinyl(lower)alkyl or (lower)alkoxy(lower)alkylmorpholinylcarbonyl-(lower)alkyl;

piperidylmethyl;

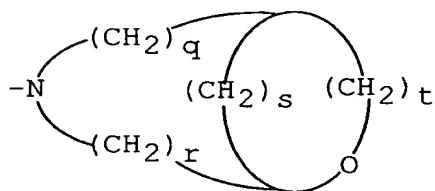
piperidyl(lower)alkyl which is substituted with lower alkyl or

(lower)alkoxy(lower)alkyl;

(2,6-dimethylmorpholino)(lower)alkyl;

(3,3-dimethylmorpholino)(lower)alkyl;

(cis-3,5-dimethylmorpholino) (lower) alkyl;
 ((3S,5S)-3,5-dimethylmorpholino) (lower) alkyl;
 (2-methoxymethylmorpholino) (lower) alkyl;
 (3-methoxymethylmorpholino) (lower) alkyl;
 5 (2-methoxymethyl-5-methylmorpholino) (lower) alkyl;
 (2-methoxymethyl-5,5-dimethylmorpholino) (lower)-
 alkyl;
 (3,5-dimethoxymethylmorpholino) (lower) alkyl;
 (2,3-dimethoxymethylmorpholino) (lower) alkyl;
 10 (2-methoxymethylmorpholino) (lower) alkenyl;
 (5,6,7,8-tetrahydro-1,6-naphthyridin-6-yl) (lower)-
 alkyl; or
 lower alkyl which is substituted with a saturated
 heterocyclic group of the formula :



(wherein
 r, s and t are each integer
 of 1 to 2, and
 q is integer of 0 to 2)

which may be substituted with one or two lower
 alkyl,
 and a salt thereof.

- 25 2. The compound of claim 1, in which
 Y is lower alkylene;
 R¹ is phenyl which may be substituted with 1 or 2
 substituent(s) selected from the group consisting
 30 of lower alkoxy, mono(or di or
 tri)halo(lower)alkyl, lower alkylthio, lower
 alkylsulfonl, di(lower alkyl)aminosulfonyl,
 pyrrolyl and pyridyl;
 R² is phenyl which may be substituted with 1 or 2
 35 substituent(s) selected from the group consisting

of lower alkyl, mono(or di or tri)halo(lower)alkyl, halogen, lower alkylenedioxy, lower alkoxy(lower)alkoxy(lower)alkoxy, hydroxy, hydroxy(lower)alkyl, cyano, pyrrolidinyl and morpholinyl which may be substituted with lower alkoxy(lower)alkyl or lower alkyl or indolyl;

R³ is hydrogen; and

R⁴ is 3-(3-pyridyl)propyl;

3-(3-pyridyl)propynyl;

(2,6-dimethylmorpholino)(lower)alkyl;

(3,3-dimethylmorpholino)(lower)alkyl;

(cis-3,5-dimethylmorpholino)(lower)alkyl;

((3S,5S)-3,5-dimethylmorpholino)(lower)alkyl;

(2-methoxymethylmorpholino)(lower)alkyl;

(3-methoxymethylmorpholino)(lower)alkyl;

(2-methoxymethyl-5-methylmorpholino)(lower)alkyl;

(2-methoxymethyl-5,5-dimethylmorpholino)(lower)-alkyl;

(3,5-dimethoxymethylmorpholino)(lower)alkyl;

(2,3-dimethoxymethylmorpholino)(lower)alkyl; or

(2-methoxymethylmorpholino)(lower)alkenyl.

3. A compound of claim 2, which is selected from the group consisting of

(1) 1-[3,5-Bis(trifluoromethyl)benzoyl]-2-[3-hydroxy-4-methylbenzyl]-4-[2-[(3R)-3-methoxymethylmorpholino]ethyl]piperazine,

(2) 1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[2-(cis-2,6-dimethylmorpholino)ethyl]-2-(3-hydroxy-4-methylbenzyl)piperazine,

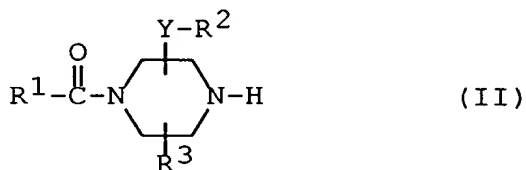
(3) 1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(3-hydroxy-4-methylbenzyl)-4-[2-[(2S,5S)-2-methoxymethyl-5-methylmorpholino]ethyl]piperazine,

(4) 1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(3-hydroxy-4-methylbenzyl)-4-[3-(3-pyridyl)-2-propynyl]piperazine,

- (5) 1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[2-[(2S)-2-methoxymethylmorpholino]ethyl]-2-(3-hydroxy-4-methylbenzyl)piperazine,
 (6) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[2-[(2S)-2-methoxymethylmorpholino]ethyl]-2-(3-hydroxy-4-methylbenzyl)piperazine, and
 (7) 1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(3-hydroxy-4-methylbenzyl)-4-[3-(3-pyridyl)propyl]piperazine,
 or a pharmaceutically acceptable salt thereof.

4. A process for the preparation of the compound of claim 1 or a salt thereof, which comprises,

- (1) reacting a compound of the formula (II) :



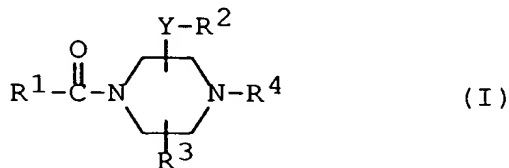
wherein R^1 , R^2 , R^3 and Y are each as defined in claim 1, or a salt thereof, with a compound of the formula (III) :



wherein R^4 is as defined in claim 1 and

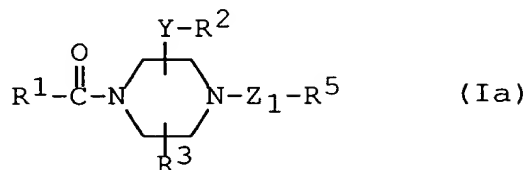
W_1 is a leaving group,

or a salt thereof to give a compound of the formula (I) :

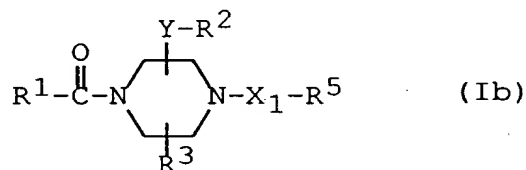


wherein R^1 , R^2 , R^3 , R^4 and Y are each as defined in
claim 1,
or a salt thereof, or

(2) subjecting a compound of the formula (Ia) :



wherein R^1 , R^2 , R^3 and Y are each as defined above,
 R^5 is 3-pyridyl, and
 Z_1 is lower alkynylene,
or a salt thereof to a reduction reaction to give a
compound of the formula (Ib) :



wherein R^1 , R^2 , R^3 , Y and R^5 are each as defined above,
and
 X_1 is lower alkylene,
or a salt thereof.

5. A pharmaceutical composition which comprises, as an active ingredient, a compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers.
6. A compound of claim 1 for use as a medicament.
7. A method for treating or preventing Tachykinin-mediated

diseases which comprises administering an effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof to human being or animals.

- 5 8. A compound of claim 1 for use as Tachykinin antagonist.
9. Use of a compound of claim 1 for manufacture of a medicament for treating or preventing Tachykinin-mediated diseases.

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